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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/955,174	09/19/2001	William G. Kerr	PH114205.2402/KMZ15101.02	9411

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EXAMINER	
ZARA, JANE J	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 10/06/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/955,174	KERR, WILLIAM G.	
	Examiner	Art Unit	
	Jane Zara	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 July 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *38-73* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *38-73* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Sequence Compliance Notice*.

DETAILED ACTION

This Office action is in response to the communication filed 7-21-04.

Claims 38-73 are pending in the instant application.

The declaration under 37 CFR 1.132 filed 7-21-04 is insufficient to overcome the rejection of claims 38-73 based upon lack or adequate written description and lack of enablement over the scope claimed as set forth in the last Office action for the reasons set forth below.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Arguments and Amendments

Withdrawn Rejections

Any rejections not repeated in this Office action are hereby withdrawn.

Maintained Rejections

Claims 38-73 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for the same reasons of record set forth in the Office action filed 2-18-04.

Applicant's arguments filed 7-21-04 have been fully considered but they are not persuasive. Applicant argues that adequate written description has been provided for the genus comprising mammalian SHIP1 mRNA because mRNA sequences encoding mouse and human SHIP1 mRNA have been publicly available in publications (e.g. cited

on pp. 2-3 of the instant specification) and in the NCBI database since 1996/1997 (as Accession Nos. NM_10566 and NM_005541). Applicants also argue that having the target gene (SHIP1) sequence, and having sufficient information in the art for the RNAi mechanism of inhibition of expression of a known target gene together represent sufficient disclosure to satisfy the written description requirement for the genus comprising RNAi specific for and inhibitory of any mammalian SHIP1 mRNA. Applicants are correct that routine experimentation is required for designing and assessing RNAi molecules that are most successful in targeting and inhibiting the expression of a known target sequence in vitro. This is not contested in the instant rejection. But, contrary to Applicant's assertions, the disclosure of a single nucleotide sequence of mouse and human SHIP1 mRNA does not provide adequate written description for the broad genus claimed. Mammalian SHIP1 mRNA includes more than a single isoform each from two species (mouse and human). The disclosure of these sequences is not representative of the broad genus. The NCBI citations provide several references, for example, of novel isoforms of SHIP2, including splice variants and ES cell specific isoforms (see e.g. Tu et al, Blood 98(7): 2028-2038; Wolf et al, Genomics 69(1): 104-112; Lucas et al, Blood 93(6): 1922-1933). Single nucleotide sequences from two mammalian species are not representative of the various sequences encompassed by the genus comprising any mammalian SHIP1 mRNA. This genus encompasses SHIP1 mRNA from other mammals (e.g. monkey, rabbit, horse...), and encompasses existing isoforms within a given species. Therefore, the rejection for

lacking adequate written description for the genus comprising mammalian mRNA of SHIP1, and corresponding RNAi, is maintained.

Claims 38-66 are rejected under 35 U.S.C. 112, first paragraph, because the specification as filed, while being enabling for a method for suppressing the rejection of a fully allogeneic bone marrow graft from BALB/C mice in SHIP-/- mice and abrogating GVHD disease in SHIP-/- mice that were transplanted with whole bone marrow from BALB/C mice, thereby enhancing SHIP-/- mice survival, does not reasonably provide enablement for reducing function of any mammalian SHIP1 in vitro or in vivo; altering NK function in a mammal; preventing a transplant rejection in any patient; or for preventing or treating graft versus host disease (GVHD) in any patient comprising the administration of an interfering RNA (RNAi) specific for any mammalian SHIP1 mRNA. The specification as filed does not teach any nucleotide sequences encoding SHIP1, nor does it teach any RNAi or other inhibitory sequences that specifically target and inhibit the expression of a target SHIP1 of disclosed nucleic acid sequence in vivo.

Applicant argues that the animal models provided in C. elegans, zebrafish, Drosophila and mammalian cell culture (as taught previously by Zamore et al and Svoboda et al, cited on p. 2 of Dr. Kerr's declaration filed 7-21-04) using RNAi provide particular guidance resolving issues associated with in vivo delivery of oligonucleotides and treatment effects. Contrary to Applicant's assertions, the examples provided pertaining to RNAi in systems such as C. elegans, zebrafish and Drosophila are not representative or correlative of the ability to target appropriate target cells harboring

SHIP1 mRNA in a mammal. The in vivo systems of these lower organisms are significantly different from mammals, and, while the RNAi results provided in these systems are encouraging for studying the roles of particular target genes thought to be related or analogous in higher organisms, they are not predictive of successful in vivo targeting and inhibition, and further whereby treatment effects are provided in a mammal. In addition, the in vitro targeting and inhibition of the same target gene (SHIP1) in mammalian cell culture (including ES cells as described on p. 3 of Dr. Kerr's declaration, filed 7-21-04) are not representative of in vivo targeting and inhibiting any mammalian SHIP1 in an organiam. In vitro results cannot be extrapolated to in vivo gene inhibition and subsequent treatment effects. In vivo results require undue experimentation, and cannot be generalized from a test tube (or cell culture) to an organism.

Applicant argues that the instant specification reviews existing gene delivery vehicles that can be used to deliver nucleic acids that target and reduce SHIP function according to the subject invention. Contrary to Applicant's assertions, a review of existing gene delivery vehicles for performing experiments in the future is not enabling for the full scope claimed. It is noted that Applicant will not have to reinvent the wheel in order to discover new gene delivery devices, and many are available and well known in the art. It is also noted that those already employed successfully by Applicant (e.g. using the RNAi molecules labeled #1 and #4, and the antisense vector used to inhibit mouse SHIP1 in vivo as described in the declaration filed 7-21-04) are enabled, but these are not representative of the broad scope claimed.

Applicant also argues that the in vivo results obtained in mice using the RNAi sequences #1, #4 and the mouse antisense vector muSHIPshRNA provided in the declaration by Dr. Kerr, filed 7-21-04 are representative and correlative of the ability to successfully target and inhibit expression of any mammalian SHIP1 mRNA in an organism and provide treatment effects such as altering NK function in a mammal, preventing a transplant rejection in any patient, and preventing or treating graft versus host disease (GVHD) in any patient comprising the administration of an interfering RNA. The RNAi sequences disclosed in Dr Kerr's declaration were not provided in the original disclosure at time of filing and therefore would constitute new matter. And, contrary to Applicant's assertions, the success of two RNAi's in their ability to target and successfully inhibit expression of the target gene encoding SHIP1 in a mouse model, and provide for an observed increase in Mac+Gr1 monocytes and circulating Mac1+GR1+cells (myeloid suppressor cells) is not representative of providing other treatment effects including altering NK function, preventing transplant rejection in any patient, or preventing or treating graft versus host disease (GVHD) in any mammal. The ability to obtain the extent of target gene inhibition (in appropriate target cells in a particular organism) using a particular RNAi for obtaining these various treatment effects requires undue experimentation beyond that taught in the instant disclosure, and cannot be substituted with the other phenotype obtained (i.e. myeloid suppressor cell increase). Applicant argues that because the SHIP1 ablation experiments provide for such phenotypes as altered NK cell function and GVHD, there is no reason to doubt that reduction of SHIP1 function by RNAi or other means of SHIP1 inhibition will be of

therapeutic benefit in suppressing transplant rejection and GVHD in mammals. Applicants are correct that the ablation experiments show promise for the therapeutic capability of RNAi and similar inhibitory approaches. But, in order for the full scope of the instant invention to be enabled, the results obtained using ablation experiments cannot be substituted for the unpredictable endeavor of providing treatment effects including altering NK cell function and GVHD in any mammal using any RNAi targeting any mammalian SHIP1 mRNA. It is still highly unpredictable that complete ablation will be obtained using these inhibitory molecules, and a measure of the extent of target gene inhibition required to achieve this treatment effect (observed in an ablated mouse model) must be determined empirically and therefore requires undue experimentation. Therefore, the instant rejection for lacking enablement over the broad scope claimed is maintained.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone number for the Group is **703-872-9306**. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(571) 272-0765.** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on (571) 272-0760. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (571) 272-0564. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

JOHN L. LeGUYADER
SUPERVISORY PATENT EXAMINER
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JZ
9-26-04